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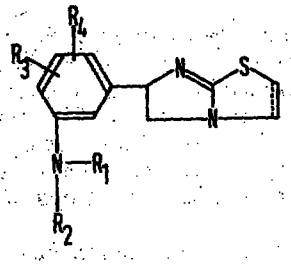
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(54) 6-(AMINOPHENYL)-5,6-DIHYDRO- OR 2,3,5,6-TETRAHYDROIMIDAZO[2,1-b] THIAZOLES

(71) We, AMERICAN CYANAMID COMPANY, a corporation organised and existing under the laws of the State of Maine, United States of America, of Berdan Avenue, Township of Wayne, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

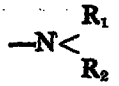
This invention relates to novel 6-(mono, di- and tri-substituted phenyl)-5,6-dihydro or 2,3,5,6-tetrahydroimidazo[2,1-b]thiazoles, to processes for their preparation, and to the use of the novel compounds in the treatment of gastro intestinal nematodes in warm-blooded animals.

In accordance with the present invention we have found that effective and safe control of gastrointestinal nematodes in warm-blooded animals can be obtained with a group of novel *dl* and *l* compounds of formula I below and their pharmaceutically acceptable salts.



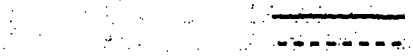
I

R_1 and R_2 are hydrogen; alkyl C_1—C_{10}; alkenyl C_2—C_8; cycloalkyl C_3—C_7; hydroxyloweralkyl; loweralkanoyloxyloweralkyl; loweralkoxyloweralkyl; benzyl; substituted benzyl; phenylethyl; substituted phenylethyl; mono- and dinitrophenyl; 2- and 4-pyridyl; 2- and 4-pyrimidinyl; 2-thiazolyl; pyridylmethyl; furfuryl; tetrahydrofurfuryl; R_5—C(O) wherein R_5 is hydrogen; alkyl C_1—C_9; alkenyl C_2—C_7; cycloalkyl C_3—C_7; haloalkyl C_1—C_8, aminoalkyl C_1—C_6, monoloweralkylaminoloweralkyl; diloweralkylaminoloweralkyl; piperidinoloweralkyl; pyrrolidinoloweralkyl; morpholinoloweralkyl; loweralkoxyloweralkyl; phenyl; substituted phenyl; furyl; tetrahydrofuryl; naphthyl; alkoxy C_1—C_8; amino, monoloweralkyllamino; diloweralkylamino; piperidino; pyrrolidino; and morpholino; or where



[*Price 25p*]

taken together represents piperidino; pyrrolidino, or morpholino ring or group (lower-alkyl)$_2$NCH=N—; and R_3 and R_4 are hydrogen, halogen or nitro; it being understood that the term " substituted " is intended to refer to monohalo, dihalo, trihalo, mononitro, dinitro, monoloweralkyl, diloweralkyl, triloweralkyl, monoloweralkoxy, diloweralkoxy and triloweralkoxy, and the terms " halogen " or " halo " refer to fluoro, chloro, bromo, or iodo; with the proviso that when R_3 and R_4 are both hydrogen not more than one member from the group R_1 and R_2 can be hydrogen,



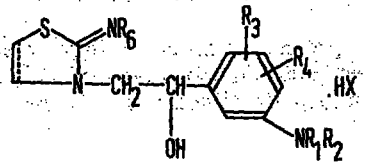
is a single or double bond. The term " lower " is intended to refer to those groups having 1 to 4 carbon atoms.

The preferred compounds of the present invention may be categorized as follows: (1) compounds of the above formula wherein R_1 and R_2 are as described above and R_3 and R_4 are each hydrogen; (2) compounds of the above formula wherein R_1 and R_2 are as described above, one of R_3 and R_4 is hydrogen and the other is halogen or nitro and is attached to the carbon in either the 4 position or the 6 position of the ring; and (3) compounds of the above formula wherein R_3 and R_4 are both hydrogen or where one of R_3 and R_4 is a halogen or nitro group attached to the carbon at the 4 or 6 position of the ring and



represents lower alkylamino, diloweralkylamino, formylamino, formylloweralkylamino, lower alkoxy carbonylamino, lower alkylamino carbonylamino, benzoyl, or lower alkanoylamino.

Several routes are available by which the compounds of this invention can be prepared. One method involves reacting a compound of the formula

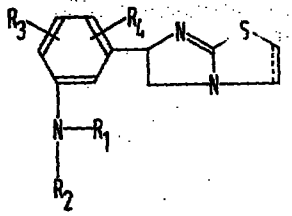


II

where R_1, R_2, R_3, R_4 are as described above and R_6 is hydrogen or lower alkanoyl e.g. acetyl and X is an anion, with (a) concentrated sulfuric acid and treating the thus-formed product with an alkali metal hydroxide or ammonium hydroxide, or (b) thionyl chloride at a temperature of from 40° C. to 75° C. and treating the reaction product with acetic anhydride at 50° C. to 140° C., removing excess lower alkanoyl anhydride from the thus-formed product, treating the product with strong mineral acid and then treating the acid solution with an alkali metal hydroxide or ammonium hydroxide to yield the desired product.

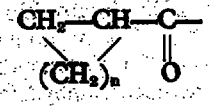
Compounds of the present invention can also be prepared using as starting material 6-(*m*-aminophenyl)-2,3,5,6,-tetrahydroimidazo[2,1-b]thiazole. The *dl* 6-(*m*-aminophenyl)-2,3,5,6-tetrahydro[2,1-b]thiazole can be resolved into the *d* and *l* isomers by using the method described in United States Patent Nos. 3,673,205 and 3,463,786, and the *l*-isomer can be used in the same manner as the racemic form as an intermediate. Thus, the *m*-aminophenyl compound can be acylated, alkylated or treated with an appropriate anhydride to produce desired compounds. The reaction can be carried out at a temperature of from 20° C. to 120° C. usually in the presence of a solvent.

Another useful process for preparing compounds of the formula:



III

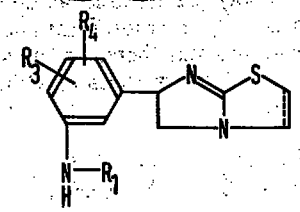
wherein R_1 is hydrogen or alkyl (C_8—C_{10}) and R_2 is lower alkanoyl,



(n is 1—5), benzoyl or loweralkoxycarbonyl, R_3 and R_4 are individually hydrogen halogen or nitro, and

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is as defined above, comprises reacting a compound of the formula:



wherein R_1, R_3 and R_4 ore as defined above, with an appropriate acid chloride or anhydride.

Other useful methods for preparing compounds of this invention will be given in the Examples hereinafter.

The compounds of the present invention are useful as anthelmintic agents effective for treating helminthiasis in warm-blooded animals. Many of the compounds tested are effective at relatively low dosage levels, for example at from 1 to 10 mg./kg of body weight of the animal being treated. The active compounds may be administered orally or parenterally.

The following examples describe in detail the preparation of compounds of this invention and the testing of representative compounds against helminths in warm-blooded animals.

Example 1.

Preparation of 6 - (*m* - isopropylaminophenyl) - 2,3,5,6 - tetrahydroimidazo [2,1 - b]-thiazole.

5.0 g. (0.023 mole) of the free base of imidazo[2,1-b]thiazole 2,3,5,6-tetrahydro-6-(*m*-aminophenyl)dihydrochloride, (*m*-aminotetramisoledihydrochloride) is dissolved in a mixture of 40 ml. of methanol and 20 ml. of 1 *N* sodium acetate water solution. The pH of the solution is adjusted to 6—7 (slightly acid) with addition of acetic acid (2 ml.) and the solution is then added to 8.5 g. (0.05 mole) of 2-iodopropane. The mixture is refluxed for 48 hours. After cooling, the excess 2-iodopropane and methanol is evaporated on a rotary evaporator. The residue is then partitioned between 100 ml. chloroform and 50 ml. water. With stirring and cooling, the system is made basic (pH 10) by the addition of sodium hydroxide solution. The chloroform layer is removed, and the aqueous layer is washed with (2 × 75 ml. portions) of chloroform. The chloroform extracts are dried over magnesium sulfate and the chloroform evaporated to yield a white solid, melting point 47—51° C. The isopropylated product is then dissolved in 150 ml. acetone and a solution of hydrogen chloride-acetone is added. The hydrochloride salt as an acetone solvate precipitate from the solution. The salt is filtered to yield 2.2 g. (0.056 mole, 25% yield) of a white solid, melting point 80—170° C.

Calcd.:	C, 42.83;	H, 5.40;	N, 10.71;	S, 8.17;	Cl, 18.07
Found:	C, 43.78;	H, 5.55;	N, 10.85;	S, 8.47;	Cl, 18.29.

Example 2.

Preparation of 6 - [*m* - (isopropylmethylamino)phenyl] - 2,3,5,6 - tetrahydroimidazo-[2,1-b]thiazole.

The above compound is prepared in a manner similar to Example 1 by alkylating 3'-N-methyl-*m*-aminotetramisole with 2-iodopropane in a water-methanol solution. The product which is very hygroscopic has infrared and nmr spectra consistent with what was expected for the product.

Example 3.

Preparation of N - isopropyl - 3' - (2,3,5,6 - tetrahydroimidazo[2,1-b]thiazol - 6 - yl) formanilide dihydrochloride.

To 4.0 g. (0.015 mole) of the 3'-N-isopropyl-*m*-amino tetramisole derivative, Example 1, is added 25 ml. of acetic-formic anhydride. The mixture is heated on a steam bath overnight (14 hrs.). The excess anhydride is then removed under reduced pressure and the residue is taken up in 50 ml. of chloroform. The chloroform solution is washed (3 × 75 ml.) with water. The water washings are combined and 100 ml. chloroform is added. The mixture is made basic (pH 10 with sodium hydroxide solution and the chloroform layer separated. The aqueous layer is extracted with 2 × 100 ml. portions of additional chloroform. The chloroform extracts are combined, dried over magnesium sulfate and the solvent removed under reduced pressure to yield 2.6 g. of a thick oil. The formylated product is purified by column chromatography (silica gel, chloroform and 10% methanol/$CHCl_3$ used as elutants). The hydrochloride salt is prepared by dissolving the free base in chloroform and bubbling in gaseous hydrogen chloride. The salt did not precipitate and therefore the salt is isolated by removing the chloroform under reduced pressure. The crystalline, white solid, melting point 55—70° C. is found to be very hygroscopic.

Calcd.:	C, 47.37;	H, 6.10;	N, 11.04;	S, 8.43;	Cl, 18.64
Found:	C, 47.76;	H, 4.98;	N, 10.68;	S, 8.14;	Cl, 17.32.

Example 4.

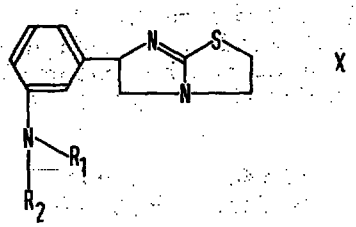
Preparation of 3' - (2,3,5,6 - tetrahydroimidazo[2,1 - b]thiazol - 6 - yl) - isobutyranilide hydrochloride.

2.2 g. (0.010 mole) of *m*-aminotetramisole is dissolved in a mixture of 15 ml. methanol and 15 ml. water and the pH is adjusted to about 6 with an aqueous hydrochloric acid solution. This solution is then added to 3.2 g. (0.020 mole) of isobutyric anhydride. The mixture is allowed to stand at room temperature for 12 hours. The reaction mixture is then added to a mixture of 100 ml. methylene chloride and 50 ml. water and then made basic (pH 10) with aqueous sodium hydroxide. The methylene chloride layer is removed and the water layer is washed twice with 75 ml. of fresh methylene chloride. The methylene chloride extracts are then combined, dried over magnesium sulfate, and the methylene chloride evaporated leaving a tacky solid. The free base of the product is recrystallized from a chloroform-ethyl ether mixture. The yield is 1.6 g. (55%). The hydrochloride salt is prepared by dissolving the free base in methanol and adding an excess of hydrogen chloride gas. The methanol is then removed on the rotary evaporator to yield a glassy white solid, melting point 125—140° C.

Calcd.:	C, 52.39;	H, 6.45;	N, 12.22;	S, 9.32;	Cl, 10.31
Found:	C, 52.40;	H, 6.25;	N, 12.32;	S, 9.46;	Cl, 10.57.

Examples 5—11.

Following the procedure of Examples 3 and 4 and reacting *dl*- or *l*- *meta*-aminotetramisole with the appropriate acid chloride or anhydride compounds of the following structure are obtained.



$-NR_1R_2$	X	Melting point	Melting point Free base	Analysis calculated	Analysis found
HN–CO–CH_2CH_3 D–L 5	HCl	120–130	120–122	C 50.97 H 6.11 N 12.74 S 9.72 Cl 10.75	C 51.02 H 6.02 N 12.96 S 9.68 Cl 10.98
HN–CO–$CH_2CH_2CH_3$ D–L 6	HCl	112–122	92–93	C 52.39 H 6.45 N 12.22 S 9.32 Cl 10.31	C 52.44 H 6.37 N 12.36 S 9.21 Cl 10.41
HN–CO–$CH(CH_3)_2$ D–L 7	HCl	110–130	–	–	–
HN–CO–$C(CH_3)_3$ D–L 8	HCl	145–160	109–111	C 53.67 H 6.76 N 11.74 S 8.96 Cl –	C 54.33 H 6.59 N 12.59 S 9.65 Cl –
HN–CO–$C(CH_3)_3$ L(–) 9	HCl	140–155	–	–	–
HN–CO–$CH(CH_2CH_3)_2$ D–L 10	HCl	120–135	65–73	C 54.89 H 7.05 N 11.30 S 8.62 Cl 9.53	C 54.82 H 7.03 N 11.21 S 8.68 Cl 9.59

$-NR_1R_2$	X	Melting point	Melting point Free base	Analysis calculated	Analysis found
HN–CO–C_6H_5 D–L 11	HCl	128–140	94–100	C 57.21 H 5.33 N 11.12 S 8.49 Cl 9.38	C 57.81 57.98 H 5.03 N 10.92 S 8.05 Cl 9.30

Examples 12—13.

Preparation of 3′ - (5,6 - Dihydroimidazo[2,1 - b]thiazol - 6 - yl) - privalanilide and 3′ - (5,6 - dihydroimidazo[2,1 - b]thiazol - 6 - yl) - isobutyranilide.

To a stirred solution of 2.0 g. (0.007 mole) of 6 - (*m* - aminophenoyl) - 5,6 - dihydroimidazo[2,1-b]thiazole dihydrochloride in 50 ml. of 50% aqueous methanol is added aqueous sodium hydroxide to give pH 5—6. Pivalic anhydride is added and the solution is stirred overnight at room temperature. Chloroform is added and the pH is adjusted to 9—10 with aqueous sodium hydroxide. The organic layer is separated and evaporated to dryness. The residue is slurried with ether and filtered to give 1.6 g. crude product. Recrystallization from ethyl acetate gives 0.75 g. of 3′-(5,6-dihydroimidazo[2,1-b]thiazol-6-yl)pivalanilide, melting point 163—165° C.

By the above procedure 3′-(5,6-dihydroimidazo[2,1-b]-thiazol-6-yl)isobutyranilide, melting point 175—178° C. is obtained when isobutyric anhydride is used in place of pivalic anhydride.

Example 14.

Preparation of *dl m* - (2,3,5,6 - tetrahydroimidazo[2,1 - b]thiazol - 6 - yl)carbonilic acid methyl ester, hydrochloride.

To 2.6 g. (0.009 mole) of dihydrochloride of dl *m*-aminotetramisole is added 40 ml. of a 1.0 M sodium acetate buffer. The solution (pH=4.6) is cooled in an ice bath and then 3.0 g. (0.032 mole) of methyl chloroformate is added, (2 molar excess) and the solution stirred for 15 minutes. After an additional 15 minutes at room temperature, the solution is then cooled in an ice bath and 50 ml. methylene chloride is added. The mixture is made basic with aqueous sodium hydroxide solution (pH 10).

The methylene chloride layer is separated and the water washed (2 × 50 ml.) with additional methylene chloride. The methylene chloride washings are combined, dried over magnesium sulfate and on removal of the solvent, 1.4 g. (56% crude yield) of

product as the free base is isolated. After being recrystallized from ethyl acetate the free base has a melting point of 135—138° C. The free base is converted to the hydrochloride salt by dissolving the recrystallized free base in acetone and passing dry hydrogen chloride gas through the solution. The hydrochloride salt precipitates and is recrystallized from ethanol; melting point 245—246° C.

Anal.:	C, 49.75;	H, 5.14;	N, 13.39;	S, 10.22;	Cl, 11.30
Found:	C, 49.72;	H, 5.30;	N, 13.10;	S, 9.93;	Cl, 11.02.

Example 15.

Preparation of *l* - *m* - (2,3,5,6 - tetrahydroimidazo[2,1 - b]thiazol - 6 - yl) - carbanilic acid methyl ester, hydrochloride.

Following the procedure of Example 14 substituting *l*-*m*-aminotetramisole for dl *m*-aminotetramisole the above compound is obtained having a melting point of 239—240° C. The analysis of the compound is as follows:

Anal.:	C, 49.75;	H, 5.14;	N, 13.39;	S, 10.22;	Cl, 11.30
Found:	C, 49.65;	H, 5.21;	N, 13.20;	S, 10.05;	Cl, 11.40.

Example 16.

Preparation of *l* - 6 - (5 - amino - 2 - nitrophenyl) - 2,3,5,6 - tetrahydroimidazo[2,1-b]thiazole, hydrochloride, acetone solvate.

4.3 g (0.014 mole) of the nitrate salt of *l*-N-acetyl-*m*-aminotetramisole is cooled in an acetone-dry ice bath and then 50 ml. of concentrated sulfuric acid is added. The salt dissolves in the sulfuric acid and the solution is allowed to stand at room temperature for five days. The mixture is then poured over 200 g. of ice and 300 ml. of chloroform is added. With cooling in an acetone-dry ice bath, the acid is neutralized with concentrated ammonium hydroxide and the pH is adjusted to about 10. The chloroform layer is separated and the water layer washed twice with an additional 150 ml. chloroform. The chloroform extracts are combined, washed with water, dried over magnesium sulfate and the solvent evaporated on a rotary evaporator to yield 3.3 g. of a yellow solid. The yellow solid is then heated in 50 ml. 6 *N* hydrochloric acid in a steam bath for 3 hours in order to hydrolyze the acetyl group. After cooling, 200 ml. chloroform is added and the acid neutralized with concentrated ammonium hydroxide. The pH is adjusted to 10 and the chloroform layer removed. The water layer is washed twice with an additional 100 ml. chloroform. Then the chloroform washings are combined, dried over magnesium sulfate, and the solvent removed to yield 1.5 g. of a yellow solid. The nitro compound is recrystallized from chloroform and dried; melting point 228—229° C. (dec.). The free base is converted to the hydrochloride salt by dissolving the free base in acetone and then a saturated hydrogen chloride-acetone solution is added. The hydrochloride salt precipitates out and is filtered and dried; melting point 140—210° C. The salt could not be readily recrystallized.

Anal.:	C, 46.74;	H, 5.21;	N, 15.58;	S, 8.92;	Cl, 9.86
Found:	C, 45.20;	H, 4.99;	N, 15.68;	S, 9.08;	Cl, 11.79.

Example 17.

Preparation of *dl* 6 - (3 - amino - 4 - bromophenyl) - 2,3,5,6 - tetrahydroimidazo-[2,1 - b]thiazole, hydrochloride.

On the nitration of 4-bromotetramisole (6-(4-bromophenyl)-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole) recovering the nitrated product as the free base and acidifying with hydrogen chloride 6-(4-bromo-3-nitrophenyl)-2,3,5,6-tetrahydroimidazo[2,1-b]-thiazole hydrochloride is obtained having a melting point of 227—229° C.

Analysis:

Calcd.:	C, 36.23;	H, 3.04;	N, 11.53;	S, 8.79;	Br, 21.92
Found:	C, 35.97;	H, 2.96;	N, 11.40;	S, 8.52;	Br, 22.09.

On reduction of the above nitro compound the corresponding amino compound (6-(3-amino-4-bromophenyl)-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole) is obtained as the free base having a melting point of 129—130° C.

Example 18.

Preparation of *dl* - 6 - (5 - amino - 2 - bromophenyl) - 2,3,5,6 - tetrahydroimidazo-[2,1 - b]thiazole dihydrochloride.

To 3.3 g. (0.015 mole) of *dl-m*-aminotetramisole is added 40 ml. of concentrated sulfuric acid along with 2.5 g. silver sulfate. The mixture is warmed on the steam bath to get the solids in solution. Then 2.7 g. (0.017 mole) of bromine is added slowly to the warm solution and there is an immediate formation of a white precipitate. The reaction mixture is stirred at room temperature for 12 hours and then is poured over about 100 g. of ice. The silver bromide precipitate is filtered off, the sulfuric acid solution is cooled in an ice bath, 150 ml. of chloroform is added, and the acidic solution is then carefully neutralized with concentrated ammonium hydroxide. The pH is raised to about 10, the chloroform layer is separated, and the water layer washed twice with an additional 75 ml. chloroform. The chloroform washings are dried over magnesium sulfate and the solvent removed on the rotary evaporator to yield an off-white solid, which is recrystallized from chloroform. The brominated product has a melting point of 153—156° C. The hydrochloride salt is prepared by dissolving the free base in acetone and adding hydrogen chloride gas. The white salt precipitates out and is filtered and dried; 2.6 g. (47% yield). The salt is recrystallized from ethanol and dried; melting point 170—210° C. (dec.).

Calcd.:	C, 35.60;	H, 4.02;	N, 11.32;	S, 8.64	
Found:	C, 36.94;	H, 4.02;	N, 10.75;	S, 8.17.	

Example 19.

Preparation of *l* - 6 - (5 - acetylamino - 2 - bromophenyl) - 2,3,5,6 - tetrahydro-imidazo[2,1 - b]thiazole.

Following the procedure of Example 18 and substituting *l*-acetylaminotetramisole for *dl*-m-aminotetramisole the above compound is obtained having as the base a melting point of 195—197° C. An analysis the product had the following values:

Calcd.:	C, 45.89;	H, 4.15;	N, 12.35;	S, 9.43;	Br, 23.49
Found:	C, 46.15;	H, 3.85;	N, 12.50;	S, 9.45;	Br, 23.82.

Example 20.

Preparation of *l* - 6 - (5 - amino - 2 - bromophenyl) - 2,3,5,6 - tetrahydroimidazo-[2,1 - b]thiazole.

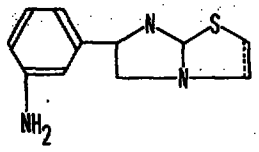
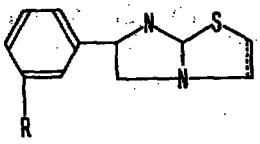
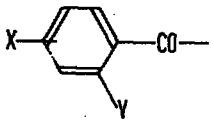
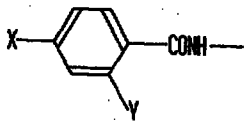
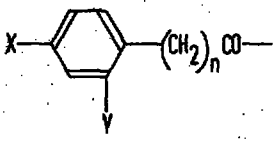
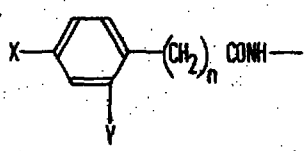
Following the procedure of Example 18 and substituting *l-m*-aminotetramisole for dl *m*-aminotetramisole the above product is obtained having a melting point of 175—177° C. An analytical sample on analysis shows

Calcd.:	C, 44.30;	H, 4.06;	N, 14.04;	S, 10.75;	Br, 26.80
Found:	C, 44.10;	H, 4.02;	N, 13.96;	S, 10.75;	Br, 26.58.

Examples 21—27.

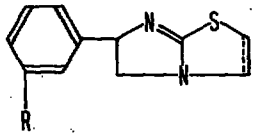
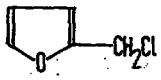
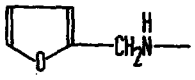
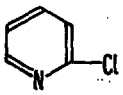
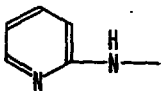
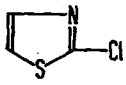
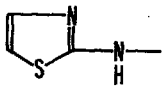
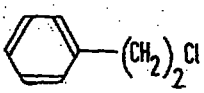
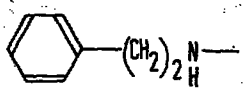
General method for acylation of 6-(m-aminophenyl)-2,3,5,6-tetrahydroimidazo-[2,1-b]thiazole and 6-(m-aminophenyl)-5,6-dihydroimidazo[2,1-b]thiazole to prepare the amide or the carbamate function.

A solution of the amino derivative in an aqueous system is treated with at least one molar equivalent of a carboxylic acid halide or anhydride or alkoxycarbamoyl chloride at a pH suitable for amide formation at the amino group but not favorable for acylation at the 7 nitrogen in the imidazo ring. After the anhydride or chloride has reacted the reaction mixture is made basic which preferentially hydrolyzes only acyl groups from the 7 position leaving only the desired compounds. Details for specific compounds are listed in Examples 4, 11, 12, 13, 14 and 15. Using these procedures the following are prepared:

Starting Material	Acylating Agent Chloride or Anhydride	Product
		
21	$CH_3(CH_2)_nCO-$	$R = CH_3(CH_2)_nCNH-$ (n = 1 to 8)
22		$R =$  (Y and X = H, lower alkyl or halogen)
23	$CH_2-CH-CO-$ $(CH_2)_n$	$R = CH_2-CH-C-NH-$ $(CH_2)_n$ (n = 1 to 5)
24		$R =$  (n = 1 to 4) (X and Y = H, halogen, lower alkyl)
25	Heterocyclic C–	$R =$ Heterocyclic C–N– (Heterocyclic = pyridyl, thiazoyly, furfuryl)
26	Alkoxy C–	$R =$ Alkoxy C–N– (C_1 to C_6)

Examples 27—32.

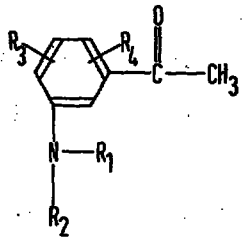
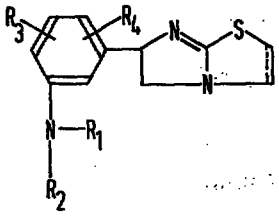
The following is a general method for alkylating 6-(*m*-aminophenyl)-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole and 6-(*m*-aminophenyl-5,6-dihydroimidazo[2,1-b]-thiazole. The procedure outlined in Example 1 is used to prepare the following 6-(alkylaminophenyl)-5,6-dihydro and 2,3,5,6-tetrahydroimidazo[2,1-b]thiazoles outlined below.

	Alkylating Agent	Product
		
27		R= 
28		R= 
29		R= 
30		R= 
31	$CH_2 = CH - CH_2X$	$R = CH_2 = CH - CH_2\overset{H}{N}-$
32	$CH_2 - CH - X$ $\backslash (CH_2)_n /$ n = 1 to 5 (X is halogen)	$R = CH_2 - CH - \overset{H}{N}-$ $\backslash (CH_2)_n /$

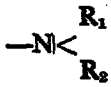
Examples 33—81.

The following are two general methods which are used for preparing the 6-(substituted phenyl)-2,3,5,6-tetrahydroimidazo[2,1-b]thiazoles and 6-(substituted phenyl)-5,6-dihydroimidazo[2,1-b]thiazoles shown in the Table below.

A. Following the procedures outlined in Examples 1—8 of U.S. Patent No. 3,673,205 a series of substituted compounds are prepared from substituted acetophenones which are prepared by the procedures described in the chemical literature. Compounds prepared by this procedure are illustrated below:

Starting Material	Final Product
	

In the case where



represents a basic function, that is a primary, secondary or tertiary amine, the starting aminoacetophenone is utilized as its hydrochloride or hydrobromide salt in the reaction with bromine to form the α-bromoacetylaniline (Example 1 of U.S. Patent No. 3,673,205);

B. Following the procedures outlined in Examples 1, 2, 4, 12, 13 and 14 above, *dl*- or *l*- *m*-amino-tetramisole is either alkylated with the appropriate alkyl, aralkyl or heterocyclic alkyl halide or acylated with the appropriate acid chloride or acid anhydride.

TABLE

Starting Material and Final Product

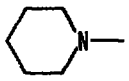
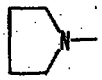
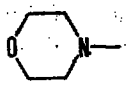
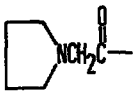
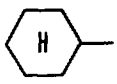
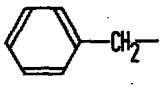
	R_1	R_2	R_3	R_4
33	CH_3	$-\overset{O}{\overset{\|\|}{C}}CH(CH_3)_2$	H	H
34	H	$-\overset{O}{\overset{\|\|}{C}}CH(CH_3)_2$	$-NO_2(5)$	H
35	H	H	H	Br(6)
36	4-pyridyl	$-\overset{O}{\overset{\|\|}{C}}-CH_3$	H	H
37	2-thiazoyl	$-\overset{O}{\overset{\|\|}{C}}-CH_3$	H	H
38	$-NR_1R_2$ =		H	H
39	$-NR_1R_2$ =		H	H
40	$-NR_1R_2$ =		H	H
41	$C_8H_{17}O\overset{O}{\overset{\|\|}{C}}-$	H	H	H
42	$CH_3OCH_2CH_2-$	$(CH_3)_2CH-$	H	H
43		H	H	H
44	$CH_2 = CH-CH_2-$	H	Cl(4)	H
45		H	H	H
46		H	H	Cl(6)

TABLE (Continued)

Starting Material and Final Product

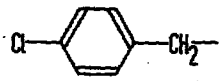
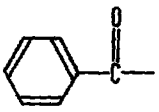
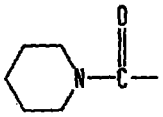
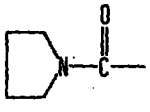
	R_1	R_2	R_3	R_4
47	$(CH_3)_2CH-$	$(CH_3)_2CHC(=O)-$	H	H
48	$CH_2=CHCH_2-$	$CH_2=CH-CH_2-$	H	H
49		H	NO_2(5)	H
50	CH_2CH_2CH-	H	H	Cl(6)
51	H	$OHCH_2CH_2-$	H	H
52	C_3H_7–*n*	C_3H_7–*n*	H	H
53	$C_2H_5C(=O)-$	H	Cl(4)	H
54	$H_2C=CH-C(=O)-$	CH_3	H	H
55	$CH_2CH_2CH_2CH-C(=O)-$, CH_2 bridge	H	H	H
56	$ClCH_2CH_2CH_2C(=O)-$	H	H	H
57		H	H	H
58	H		H	H
59	H		H	$-NO_2$(6)

TABLE (Continued)

Starting Material and Final Product

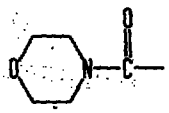
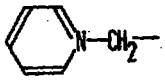
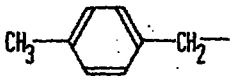
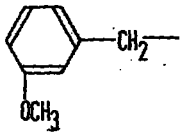
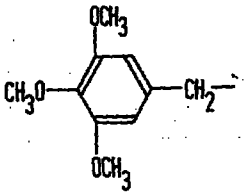
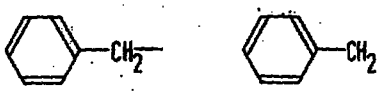
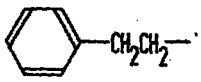
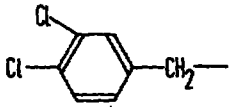
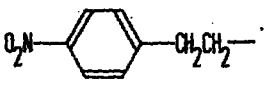
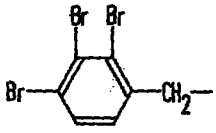
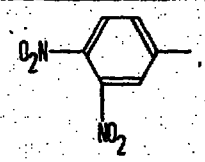
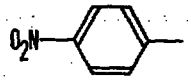
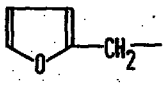
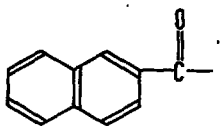
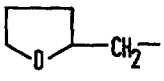
	R_1	R_2	R_3	R_4
60	H		H	H
61	H		H	H
62		H	H	H
63		H	H	H
64		H	H	H
65			H	H
66		H	H	H
67		H	H	H
68		H	$-NO_2$(4)	H
69		H	H	H

TABLE (Continued)

Starting Material and Final Product

	R_1	R_2	R_3	R_4
70		H	H	H
71		H	H	$-NO_2(6)$
72	4-pyrimidinyl	H	H	H
73	H	2-pyrimidinyl	H	H
74	H		H	H
75	H	$C_2H_5NHC(=O)-$	H	H
76	$(CH_3)_2NCH_2C(=O)-$	H	H	H
77	$CH_3CH(OCH_3)CH_2C(=O)-$	H	H	H
78	$(CH_3)_2NC(=O)-$	H	H	H
79		H	H	H
80	$(CH_3)_2NC(H)=$	H	H	H
81	H		H	H

Example 82.

Preparation of 6 - (*m* - dimethylaminophenyl) - 2,3,5,6 - tetrahydroimidazo[2,1 - b]-thiazoledihydrochloride.

A quantity of 6.0 g. (50 mmol) of thionyl chloride is slowly added to 6.0 g. (1.8 mmol) of 3'-[1-hydroxy-2-(2-imino-3-thiazolidinyl)ethyl]dimethylanilide hydrochloride in 100 ml. chloroform and the reaction mixture is stirred for one hour at room temperature. Then 200 ml. of water is added to the reaction mixture and the pH of the solution is adjusted to 9—10 with potassium carbonate. The two-phase system is refluxed for 8 hours. The chloroform layer is separated, dried over magnesium sulfate and on removal of the solvent, 2.2 g. of a dark oil is isolated. The free base is then dissolved in acetone, acidified with hydrogen chloride and the product precipitated out. The dihydrochloride salt is filtered and dried. Yield 1.3 g. Melting point 170°—200° C. The product could not be purified by recrystallization from the usual solvents. Structure is based on a comparison of IR and NMR spectra of the compound to closely related compounds.

Example 83.

Albino female mice are each inoculated with about 20 infectious larvae of *Nematospiroides dubius*. This nematode is a representative of the economical important trichostrongylidae worms of ruminants and other hosts, and of nematodes in general. Twenty-two days after inoculation, groups of four randomly selected mice containing adult *N. dubius* are given single oral doses of test compounds dissolved or suspended in 0.4 ml. of water per 20 gram mouse. At 26 or 27 days after inoculation, treated mice and in each test four randomly selected groups of untreated mice are necropsied. The number of worms in the small intestine of each mouse are determined by microscopic examination. The does which removes 50% of the worms is identified as ED_{50}.

Data on the acute oral toxicity to mice of various single oral doses of the above compounds and several analogs were obtained by conventional procedures, (Table I hereinafter). These *m*-amino and substituted *m*-amino analogs of tetramisole are considerably more toxic than tetramisole in agreement with their higher anthelmintic activity. However, all compounds including tetramisole have a similar chemotherapeutic index, i.e., LD_{50}/ED_{50}, of ten- to twentyfold. All compounds were well tolerated at dosages required for complete worm removal.

TABLE I

Mouse Oral Toxicity of Various Tetramisoles

Phenyl Substituent	*m*–NH–CO–C_2H_5	*m*–NH–CO–C_3H_7n	*m*–NH–CO–$CH(CH_3)_2$	*m*–NH–CO–$CH(CH_3)_2$	*m*–NH–CO–$C(CH_3)_3$
Stereo Isomer	*dl*	*dl*	*dl*	*l*	*dl*
Dose Mg./Kg.			Dead/Total		
200					
160					5/6
150					
120			6/6		
100	6/6	5/5		8/8	
80	5/5	4/5	5/6		2/6
60	4/6	4/5			
50				2/8	
40	4/5	3/5	1/6		0/6
Approx. LD_{50}	<40	40	~60	50	100
Approx. ED_{50}	2	2	3	1	3
Approx. LD_{50}/ED_{50}	20	20	20	50	33

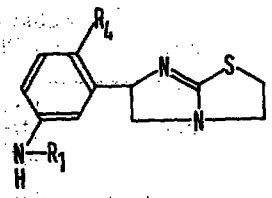
TABLE I (Continued)

Mouse Oral Toxicity of Various Tetramisoles

Phenyl Substituent	*m*–NH–CO–C(H)(CH$_3$)$_2$	*m*–NH–CO–CH(C$_2$H$_5$)$_2$	*m*–NH–CO–C$_6$H$_4$–	*m*–NH–CO–OCH$_3$	*m*–NH–CO–OCH$_3$	*m*–NH–CH(CH$_3$)$_2$
Stereo Isomer	*l*	*dl*	*dl*	*dl*	*l*	*dl*
Dose Mg./Kg.	Dead/Total					
200	6/6			5/5	5/5	
160		3/6				
150				3/5	1/5	
120		0/6	5/6			
100	2/6			0/5	0/5	5/6
80		0/6	4/6			4/6
60			3/6			3/6
50	0/6			0/5	0/5	
40			0/6			2/6
Approx. LD$_{50}$	100	160	60	150	≈150	≈40
Approx. ED$_{50}$	1	75	1	15	75	5
Approx. LD$_{50}$/ED$_{50}$	100	21	60	10	20	8

TABLE I (Continued)

Mouse Oral Toxicity of Various Tetramisoles



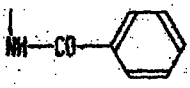
Dose Mg./Kg.	Dead/Total				
	R_1=H R_4=NO_2	R_1=H R_4=Br	R_1=$COCH_3$ R_4=Br		
240	6/6				
120	2/6				
80		6/6			
60	0/6				
40		2/6			
20		0/6			
Approx LD_{50}	120	40	>100		
Approx. ED_{50}	2	5	30		
Approx. LD_{50}/ED_{50}	60	8	>3		

Example 84.

Using the procedures of Example 83, the approximate single dose oral ED_{50} values against *N.* dubius in mice were determined for tetramisole and analogs with various substituents on its phenyl ring (Table II hereinafter). The unexpected high activity of *dl-m*-aminotetramisole is attributable to its *laevo* component; and not only amino, but also various substituted amino groups in the *meta* position increased activity over tetramisole. Identical substituents in the *para* or *ortho* positions were less active than tetramisole; as were other types of substituents in the *meta* position. Particularly noteworthy was higher quantitative activity than for the meta-nitro analogs.

TABLE II

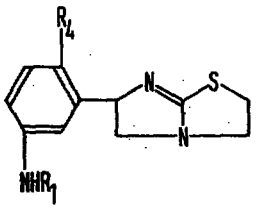
Comparative Oral Efficacy of Various Tetramisoles Against *N. dubius*

Stereo Isomer	Salt	Substituent/ on Phenyl	ED_{50} meta
dl	HCl	NH–CO–C_2H_5	2
dl	HCl	NH–CO–C_3H_7n	2
dl	HCl	NH–CO–$CH(CH_3)_2$	3
l	HCl	NH–CO–$CH(CH_3)_2$	1
dl	Base	NH–CO–$CH(CH_3)_2$	7.5
dl	HCl	NH–CO–$C(CH_3)_3$	3
l	HCl	NH–CO–$C(CH_3)_3$	1
dl	Base	NH–CO–$C(CH_3)_3$ *	7.5
dl	HCl	NH–CO–CH–$(C_2H_5)_2$	7.5
dl	HCl		1
dl	HCl	NH–CO–OCH_3	15
l	HCl	NH–CO–OCH_3	7.5
dl	HCl	NH–$CH(CH_3)_2$	5

* This compound, 5,6-dihydro imidazothiazole – all others 2,3,5,6-tetrahydro.

TABLE II (Continued)

Comparative Oral Efficacy of Various Tetramisoles Against *N. dubius*



Stereo Isomer	Salt	R_1	R_4	ED_{50}
dl	HCl	H	NO_2	2
dl	HCl	H	Br	5
dl	HCl	$-COCH_3$	Br	30

Example 85.

Dogs infected with mature adult whipworms *Trichuris vulpis* were treated with various single or double doses of unsubstituted or substituted tetramisole analogs by the oral or subcutaneous route (Table III hereinafter). Whipworms passed in the feces were collected for several days, and the whipworms still present determined at necropsy. Percent effcacy was determined in these " critical " tests. The *meta*-amino analogs had surprisingly higher activity than unsubstituted tetramisole with oral or subcutaneous doses which were non-toxic for the dogs. *Trichuris* is a type of nematode refactory to treatment with most prior anthelmintics at well tolerated doses. Taxonomically allied nematodes, e.g., Trichinella and Capillaria are also refractory to most anthelmintics.

TABLE III

Comparative Oral or Subcutaneous (SC) Activity vs. Mature *Trichuris vulpis* in Dogs

Stereo Isomer	Meta Substituent on Phenyl	Maximum Non-Lethal Dose for Dog Mg/Kg		% Efficacy Orally			% Efficacy SC					
		Oral	SC	5	2.5	1.25 (Mg/Kg)	20	15	10	5	2.5	1.25 (Mg/Kg)
dl	H	>20	25	✱10 mg/kg)[a]			–	–	2 (3)	–		
l	H		30	–			100 (2)[x]	43 (2)[x]	50 (7)	8 (2)	–	
dl	NH_2	7.5	5	98	99 (2)				–	100 (3)[y]	92 (2)	–
l	NH_2	10	4	100	100 (2)	94 (3)				–	100 (2)	72 (4)
dl	NH–HCO	7.5	>5	100	83 (2)	21						
l	NH–HCO	>2.5			100 (2)	46 (4)[b]						
dl	$NH–CH_3$	>10	30	100						94	29	

a. Other values in ( ) equal number of dogs when more than one. % Efficacy based on total worms removed and present in all dogs at each dose shown.

✱ Means inactive at dose shown.

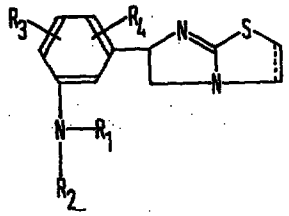
b. Average dose 1.5 (1.25–1.75).

x. Total dose given twice a day.

y. Two dogs single dose, other total dose twice a day.

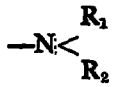
WHAT WE CLAIM IS:—

1. The racemic or levorotatory isomer of a compound of the formula:

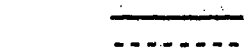


I

wherein R_1 and R_2 are the same or different and each is hydrogen; alkyl C_1—C_{10}; alkenyl C_2—C_8; cycloalkyl C_3—C_7; hydroxyloweralkyl; loweralkanoyloxyloweralkyl, loweralkoxyloweralkyl; benzyl, substituted benzyl, phenylethyl; substituted phenylethyl; mono- or dinitrophenyl; 2- or 4-pyridyl; 2- or 4-pyrimidinyl; 2-thiazolyl; pyridylmethyl; furfuryl; tetrahydrofurfuryl or R_5—C(O) wherein R_5 is hydrogen; alkyl C_1—C_9; alkenyl C_2—C_7; cycloalkyl C_3—C_7; haloalkyl C_1—C_6; aminoalkyl C_1—C_6; monoloweralkylaminoloweralkyl; diloweralkylaminoloweralkyl; piperidinoloweralkyl; pyrrolidinoloweralkyl; morpholinolowerakyl; loweralkoxyloweralkyl; phenyl; substituted phenyl; furyl; tetrahydrofuryl; naphthyl; alkoxy C_1—C_8; amino; monoloweralkylamino; diloweralkylamino; piperidino; pyrrolidino or morpholino; or



taken together represents piperidino; pyrrolidino or morpholino ring or the group $(loweralkyl)_2$—NCH=N—; and R_3 and R_4 are the same or different and each is hydrogen; halogen; or nitro; the term "substituted" refers to monohalo; dihalo; trihalo; mononitro; dinitro; monoloweralkyl; diloweralkyl; triloweralkyl; monoloweralkoxy; diloweralkoxy; or triloweralkoxy; the terms "halogen" or "halo" refer to fluoro; chloro; bromo; or iodo; the term "lower" refers to groups having 1 to 4 carbon atoms; with the proviso that when R_3 and R_4 are both hydrogen not more than one member from the group R_1 and R_2 can be hydrogen;



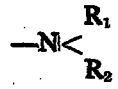
is a single or double bond; or a pharmaceutically acceptable salt of the compound of Formula I.

2. A compound according to Claim 1, wherein R_3 and R_4 are both hydrogen.

3. A compound according to Claim 1, wherein R_4 is hydrogen, and R_3 is a halogen attached to the carbon in the 4- or 6- position of the ring.

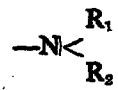
4. A compound according to Claim 1, wherein R_4 is hydrogen, and R_3 is a nitro group attached to the carbon in the 4- or 6-position of the ring.

5. A compound according to Claim 1, wherein R_3 and R_4 are both hydrogen or one or R_3 and R_4 is a halogen or nitro group attached to the carbon at the 4- or 6-position, and



is loweralkylamino; diloweralkylamino, formylamino, formylloweralkylamino, loweralkoxycarbonylamino; loweralkylaminocarbonylamino, benzoyl or lower alkanoylamino.

6. A compound according to Claim 1, wherein



is loweralkylamino.

7. A compound according to Claim 6, wherein

$$-N\langle^{R_1}_{R_2}$$

is methylamino.

8. A compound according to Claim 1, wherein

$$-N\langle^{R_1}_{R_2}$$

is formylamino.

9. A compound according to Claim 1, wherein

$$-N\langle^{R_1}_{R_2}$$

is isobutyrylamino.

10. A compound according to Claim 1, wherein

$$-N\langle^{R_1}_{R_2}$$

is amino and R_3 is bromo.

11. A compound according to Claim 1, wherein

$$-N\langle^{R_1}_{R_2}$$

is benzoylamino.

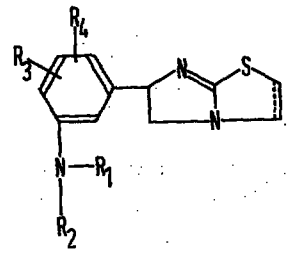
12. A compound according to Claim 1, wherein R_3 and R_4 are hydrogen,

---

is a single bond, and $-NR_1R_2$ is one of the following groups:

$-NHCOCH(CH_3)_2$,
$-NHCOC(CH_3)_3$, and
$-NHCOC_6H_5$.

13. A process for the preparation of a compound having the formula:

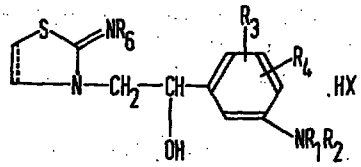


I

wherein R_1, R_2, R_3, R_4 and

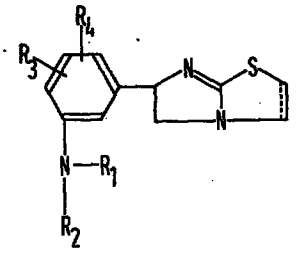
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are as defined in Claim 1, comprising reacting a compound of the formula:



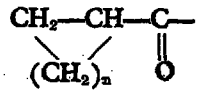
wherein R_1, R_2, R_3, R_4 are as defined in Claim 1, R_6 is hydrogen or loweralkanoyl and X is an anion; with (a) concentrated sulfuric acid and treating the thus-formed product with an alkali metal hydroxide or ammonium hydroxide, or (b) thionyl chloride at a temperature of from 40° C. to 75° C. and treating the reaction product with acetic anhydride at 50° C. to 140° C., removing excess loweralkanoyl anhydride from the thus-formed product, treating the product with strong mineral acid and then treating the acid solution with an alkali metal hydroxide or ammonium hydroxide to yield the compound of formula I.

14. A process for the preparation of a compound of the formula:



III

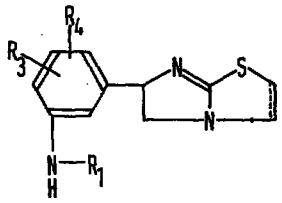
wherein R_1 is hydrogen or alkyl (C_3—C_{10}) and R_2 is loweralkanoyl,



(n=1—5), benzoyl or loweralkoxycarbonyl, R_3 and R_4 are hydrogen, halogen or nitro, and

---

is a single or double bond, comprising reacting a compound of the formula:



wherein R_1, R_3, R_4 and

---

are as defined above, with an appropriate acid chloride or anhydride.

15. A method for controlling gastrointestinal nematodes in warm-blooded animals (other than human beings), comprising administering a nematocidally effective amount of a compound according to any one of Claims 1—12.

16. A method according to Claim 15, wherein said compound is administered orally at from 1 to 10 mg./kg. of body weight of said animal.

17. A method according to Claim 15, wherein said compound is administered parenterally at from 1 to 10 mg./kg. of animal body weight.

18. A compound of formula I, substantially as described in any one of the Examples herein.

19. A process for the preparation of a compound of formula I, substantially as described in any one of the Examples 1 to 82 herein.

20. A compound of formula I whenever prepared by a process according to any one of Claims 13, 14 or 19.

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